REMARKS

Favorable reconsideration is respectfully requested.

The claims are 1, 2, 5, 7 and 9-12.

Claims 1, 2, 5, 7 and 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yanagawa (U.S. 6,197,328 B1) or Yanagawa (EPO 0 681 833 A2).

This rejection is respectfully traversed.

The formulation for the nasal administration of insulin of the present invention has the following characteristic features, as recited in claim 1:

a) "Porous, spherical calcium carbonate as a carrier of insulin" has:

a1) "a relative (or specific) surface area of 1.5 m^2/g or greater (BET method)",

a2) "a particle diameter substantially in the range of 20-32 μm" and

b) "insulin is adsorbed or carried on said carrier as a monolayer or multilayer".

Citing Yanagawa (U.S. '328) in the pending Official Action, the rejection states in connection with the present invention:

> "...Yanagawa teaches a mean particle size of the porous calcium carbonate to be 15-300 microns (Applicant's range is 20-32 microns)...The particle surface area of calcium carbonate taught by Yanagawa is from 0.1 m^2/g to 0.4 m^2/g (Applicant's range is 1.5m^2/g or greater)."

The rejection further indicates that, in Test Example 2 in column 5 of Yanagawa (U.S. '328), there is used calcium carbonate which has a mean particle size of 20-45 μm.

Thus, the rejection states:

> "The surface area taught is slightly less than Applicant's claimed surface area, however, it would have been obvious to one of ordinary skill in this art that suitable ranges or amounts could be determined through routine or manipulative experimentation to obtain the best possible results, as these are indeed variable parameters."

The above statement is untenable.

In the present specification at page 6, lines 6-8, it is disclosed:

> "This is significantly higher than that of standard light calcium carbonate available on the market, which is usually 0.1-0.3 m^2/g." (Emphasis added)

When the above-mentioned surface area of 0.1-0.3 m^2/g is compared with a surface area of from 0.1 m^2/g to 0.4 m^2/g of carrier which is employed in Yanagawa (U.S. '328), it is considered that Yanagawa (U.S. '328) uses said standard, commercially available light calcium carbonate.

The calcium carbonate which is used in the present invention, on the other hand, is obtained only through the classification of such unique particles as defined in the present specification at page 4, line 3 to page 5, line 17, and cannot be produced easily by the classification of standard, commercially available light calcium carbonate.

This would be understood from Table 1 and Figure 1 in Referential material 1 of the Rule 132 Declaration by Dr. Shunji Haruta, which is enclosed herewith, and from Section 3 of said Declaration.

Owing to the use of such a unique calcium carbonate as a carrier of insulin, the present invention shows excellent bioavailability of insulin which could never have been foreseen from Yanagawa (U.S. '328) and Yanagawa (EPO '833 A).

Please see Figure 2 and Sections 4 and 5 of the above-mentioned Declaration. In the light of said Section 4, said Figure 2 demonstrates the following:

Serum insulin concentrations of 50 IU/50 mg $CaCO_3$/5 mg HPC-H formulation conducted as Test Example 2 in Yanagawa (U.S. '328), is significantly lower than those of 48 IU/48 mg PC-$CaCO_3$ conducted by the Applicant, despite the addition of HPC-H as an absorption accelerator to the $CaCO_3$ carrier. It should be appreciated that serum insulin concentrations of 100 IU/50 mg $CaCO_3$ formulation (without HPC-H as an absorption accelerator) conducted as Test Example 2 in Yanagawa (U.S. '328) is <u>enormously lower than those of 48 IU/48 mg PC-$CaCO_3$ formulation conducted by the Applicant, despite twice the insulin dose of Yanagawa (U.S. '328)</u>.

In other words, 48 IU/48 mg PC-$CaCO_3$ formulation based on the present invention enables a higher maximum insulin concentration (approximately 1.5 fold) without HPC-H as an absorption accelerator when compared with 50 IU/50 mg $CaCO_3$/5 mg HPC-H formulation conducted in Yanagawa (U.S. '328) and <u>enables a much higher maximum insulin concentration</u> (approximately 4-8 fold despite the twice insulin dose of Yanagawa (U.S. '328) when compared

with 100 IU/50 mg $CaCO_3$ formulation without HPC-H, prepared by using $CaCO_3$ with the particle size of 20-45 μm and the specific surface area of 0.1 m^2/g to 0.4 m^2/g.

Considering the approximate particle size range between PC-$CaCO_3$ (20-32 μm) of Applicant and $CaCO_3$ (20-45 μm) conducted as Test Example 2 in Yanagawa (U.S. '328), it is apparent that the difference of insulin absorbability between the two results from the difference in specific surface areas between the two.

It is apparent from the above that the rejection errs in saying, with regard to calcium carbonate as a carrier in Yanagawa (U.S. '328), "The surface area taught is slightly less than Applicant's claimed surface area".

With respect to Yanagawa (EPO '833A), the invention of which had been made by Yanagawa prior to Yanagawa (U.S. '328), the rejection states as follows:

"...Yanagawa teaches similar or overlapping ranges for the particle size and is silent as to the specified surface area." (emphasis added)

In reply, Yanagawa did not consider that the specific surface area of carrier would play a critical role in the nasal administration of drugs.

Hence, paying no attention to the specific surface area of the carrier, Yanagawa proposed to use an absorption accelerator and HPC-H together.

Therefore, it is apparent that the present invention is unobvious over Yanagawa (EPO '833 A) and Yanagawa (U.S. '328), alone or combined.

No further issues remaining, allowance of this application is respectfully requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact undersigned at the telephone number below.

Respectfully submitted,

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